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Variant: NM_003159.3:c.2714-3861C>A

Version: 1.0

CA412370587

Gene: CDKL5 (HGNC:6792)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: a5615358-dd36-41e2-9dd0-6b80f59a7db1
Approved on: 2025/9/18
Published on: 2025/9/19

HGVS expressions

NM_003159.3:c.2714-3861C>A
NC_000023.11:g.18642146C>A
CM000685.2:g.18642146C>A
NC_000023.10:g.18660266C>A
CM000685.1:g.18660266C>A
NC_000023.9:g.18570187C>A
NG_008475.1:g.221542C>A
NG_008659.3:g.40303G>T
ENST00000379984.4:c.533G>T
ENST00000379984.3:c.533G>T
ENST00000379989.6:c.2714-3861C>A
ENST00000379996.7:c.2714-3861C>A
ENST00000476595.1:n.1024G>T
NM_000330.3:c.533G>T
NM_001037343.1:c.2714-3861C>A
NM_003159.2:c.2714-3861C>A
NM_000330.4:c.533G>T
NM_001037343.2:c.2714-3861C>A

Likely Pathogenic

Met criteria codes 3

PM5 PP3_Strong PM2_Supporting

Evidence Links 0

Expert Panel

X-linked Inherited Retinal Disease VCEP

Criteria Specification Information

Criteria Specification: *ClinGen X-linked Inherited Retinal Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RS1 Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

X-linked Inherited Retinal Disease VCEP

NM_000330.4(RS1):c.533G>T (p.Gly178Val) is a missense variant encoding the substitution of glycine with valine at amino acid 178. Another missense variant in the same codon, NM_000330.4(RS1):c.533G>A (p.Gly178Asp), (PMID: 31087526, 12928282, 31149861, 11738458, 9618178) has been classified as pathogenic for X-linked retinoschisis by the ClinGen X-linked IRD VCEP, while no benign missense variants have been identified in this codon. The present variant has a higher Grantham's distance (109) than the comparison variant (94), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5). This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.981, which is above the ClinGen X-linked IRD VCEP threshold of >0.932 and predicts a damaging effect on RS1 function (PP3_Strong). The computational splicing predictor SpliceAI gives a delta score of 0.00 for all predictive splice changes, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not predict that the variant disrupts RS1 splicing. In summary, this variant is classified as likely pathogenic for X-linked retinoschisis based on the ClinGen X-linked Inherited Retinal Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RS1 Version 1.0.0: PM2_supporting, PP3_strong, and PM5_supporting.

Met criteria codes

PM5	✔	Another missense variant in the same codon, NM_000330.4(RS1):c.533G>A (p.Gly178Asp), (PMID: 31087526, 12928282, 31149861, 11738458, 9618178) has been classified as pathogenic for X-linked retinoschisis by the ClinGen X-linked IRD VCEP, while no benign missense variants have been identified in this codon. The present variant has a higher Grantham's distance (109) than the comparison variant (94), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5).
PP3_Strong	✔	The computational predictor REVEL gives a score of 0.981, which is above the ClinGen X-linked IRD VCEP threshold of >0.932 and predicts a damaging effect on RS1 function (PP3_strong). The computational splicing predictor SpliceAI gives a delta score of 0.00 for all predictive splice changes, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not predict that the variant disrupts RS1 splicing.
PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).

Curation History

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